

## MANAGEMENT OF ASYMPTOMATIC GENE CARRIERS OF TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

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**ABSTRACT:** Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, severe, and irreversible, adult-onset, hereditary disorder caused by autosomal-dominant mutations in the *TTR* gene that increase the intrinsic propensity of transthyretin protein to misfold and deposit systemically as insoluble amyloid fibrils in nerve tissues, the heart, and other organs. TTR-FAP is characterized by relentless, progressively debilitating polyneuropathy, and leads to death, on average, within 10 years of symptom onset without treatment. With increased availability of disease-modifying treatment options for a wider spectrum of patients with TTR-FAP, timely detection of the disease may offer substantial clinical benefits. This review discusses mutation-specific predictive genetic testing in first-degree relatives of index patients diagnosed with TTR-FAP and the structured clinical follow-up of asymptomatic gene carriers for prompt diagnosis and early therapeutic intervention before accumulation of substantial damage.

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**T**ransthyretin familial amyloid polyneuropathy (TTR-FAP) is a relentless, rare, adult-onset disorder inherited as an autosomal-dominant trait with variable penetrance.<sup>1–4</sup> TTR-FAP is caused by mutations in the *TTR* gene (chromosome 18q11.2-12.1) that destabilize variant TTR protein, thereby facilitating

its misfolding and deposition as amyloid fibrils in body tissues.<sup>4</sup> The clinical picture of TTR-FAP is characterized by debilitating sensory–motor and autonomic polyneuropathy, which may be accompanied by cardiac, gastrointestinal (GI), renal, ocular, and leptomeningeal symptoms.<sup>1,5,6</sup> Initial symptoms may appear between the second and ninth decades of life.<sup>1–3</sup> Without treatment, death occurs, on average, within 7–10 years of symptom onset.<sup>7–9</sup>

Current therapies, including liver transplantation (which removes the main source of systemically circulating variant TTR protein and is beneficial in carefully selected patients)<sup>10</sup> and the oral therapeutic agent tafamidis (a highly specific TTR stabilizer approved in the European Union and several Latin American and Asian countries),<sup>11–14</sup> halt or slow the progression of TTR-FAP and are most effective when initiated during the early stages of disease.<sup>2,10,11</sup> Therefore, timely detection of sentinel signs/symptoms of TTR-FAP and prompt implementation of disease-modifying therapies may offer substantial clinical benefit.<sup>2,15</sup> In turn, identification of clinically affected individuals at the earliest possible time should be a foremost clinical objective.

In this article we discuss predictive genetic testing in relatives of index patients diagnosed with TTR-FAP, and present advice on the management of asymptomatic gene carriers based on the published literature and our experience with presymptomatic testing at 5 centers in Argentina, Germany, Italy, Mexico, and Portugal.

### PREDICTIVE GENETIC TESTING FOR TTR-FAP

After identification of the pathogenic *TTR* mutation in an index patient diagnosed with TTR-FAP, mutation-specific genetic testing in first-degree relatives allows determination of whether they carry the mutation and are at risk to develop TTR-FAP. In turn, periodic screening for early signs/symptoms of the condition in asymptomatic gene carriers can ensure timely diagnosis and

**Abbreviations:** BNP, brain natriuretic peptide; GI, gastrointestinal; HRV, heart rate variation; NSAID, non-steroidal anti-inflammatory drug; NT pro-BNP, N-terminal pro-hormone brain natriuretic peptide; PND, polyneuropathy disability; SNP, single-nucleotide polymorphism; TTR-FAP, transthyretin familial amyloid polyneuropathy

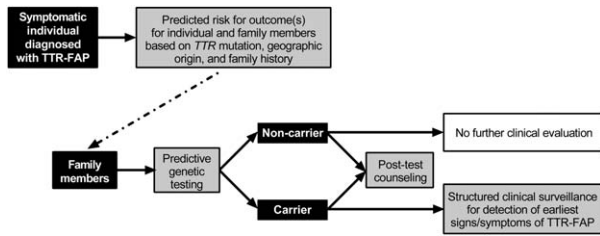
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**FIGURE 1.** Predictive genetic testing and structured clinical follow-up of carriers of TTR-FAP mutations. TTR-FAP, transthyretin familial amyloid polyneuropathy.

initiation of disease-modifying measures, thereby improving clinical outcomes (Fig. 1).

**Ethical Considerations.** The practice of genetic testing must be governed by the following primary ethical principles: respect for autonomy; beneficence (provide greatest benefit); non-maleficence (cause minimal harm); and justice (testing accessible to all).<sup>16</sup> In accordance with the principle of individual autonomy, genetic counseling should be non-directive. The decision to take a genetic test must be an autonomous personal choice; informed consent should be sought and documented.<sup>17,18</sup>

Predictive genetic testing for TTR-FAP offers many potential advantages, but is also associated with potential harm (Table 1). The risk/benefit ratio is greatly impacted by evidence-based interventions available for individuals at risk. The increased availability of oral treatment options for TTR-FAP, a non-invasive and growing alternative to liver transplant, seems to be a major trigger for at-risk adults to undergo genetic testing.<sup>19</sup> The highly specific TTR stabilizer tafamidis is the only medicine approved to delay disease progression in TTR-FAP. Another non-specific TTR stabilizer, diflunisal [a non-steroidal anti-inflammatory drug (NSAID)], is not approved to treat TTR-FAP, but it delayed disease progression in an earlier clinical trial;<sup>20</sup>

however, the risk of serious NSAID-related side effects may limit its use. Other alternatives are in various stages of development, including *TTR* gene silencing to prevent further amyloid deposition as well as amyloid fibril disrupters to clear established amyloid deposits.<sup>21,22</sup> Due to a current lack of preventive interventions at the presymptomatic stage of TTR-FAP, potential medical benefits of genetic testing will be more temporally proximal among at-risk siblings than among at-risk offspring of an index patient, as the former are at higher risk to develop clinical disease in the immediate future and may more rapidly reap benefit from current treatment options.

In our experience,  $\geq 75\%$  of people counseled about their risk of carrying a TTR-FAP mutation eventually decide that there is an advantage to being tested, with many family members requesting a test 2–3 years after diagnosis of an index case. Similarly, a Japanese nationwide survey revealed that 26 (74.3%) of 35 clients at risk for TTR-FAP who showed an interest in predictive genetic testing actually underwent the test.<sup>19</sup>

**Ethical and Psychosocial Challenges.** We review 4 challenging cases to illustrate some of the dilemmas that may be faced by physicians, patients, partners, and relatives.

**Importance of Psychological Support.** Case 1: A 50-year-old man with advanced TTR-FAP due to a *TTR* Gly47Ala (p. Gly67Ala) mutation [late stage 1 disease with polyneuropathy disability (PND) score of 2 and GI symptoms] did not want to disclose the hereditary nature of his condition to any family member, because he wanted his 20-year-old son to complete his professional training before learning about his 50% risk of carrying a TTR-FAP mutation. The father received a liver transplant 1 year later, and again requested the inherited disease risk remain undisclosed. The son finished his

**Table 1.** Potential benefits and risks of predictive genetic testing.<sup>16,17,33,53,54</sup>

Test result	Benefits	Risks
Negative	<ul style="list-style-type: none"> <li>• Relief of anxiety</li> </ul>	<ul style="list-style-type: none"> <li>• “Survivor guilt”</li> </ul>
Positive	<ul style="list-style-type: none"> <li>• Relief of uncertainty</li> <li>• Opportunity for psychological adjustment</li> <li>• Informed decision-making about the future (including family, career, financial, and personal planning)</li> <li>• Early detection of symptom onset and effective intervention with disease-modifying treatment</li> <li>• Potential improvement in clinical outcome</li> </ul>	<ul style="list-style-type: none"> <li>• Psychological issues (e.g., anxiety, guilt, self-image)</li> <li>• Altered perception by others and impact on personal relationships</li> <li>• Difficult family relations (e.g., if test result reveals information regarding family members who do not want to know their carrier status or implications of non-paternity/non-maternity)</li> <li>• Confidentiality and genetic discrimination*</li> <li>• Difficulties obtaining health and life insurance*</li> </ul>

\*The major reason for genetic discrimination in relation to Huntington’s disease appears to be family history rather than genetic testing.<sup>17</sup>

training another year later, and his father advised him to seek genetic counseling. It turned out that the son had already researched TTR-FAP on the internet without telling his father and was aware of the inherited risk. Subsequent carrier testing was positive, which resulted in the father suffering major depression. Consequent noncompliance in taking his prescribed medication culminated in his death. Any explanation of the potential benefits of new therapies for his son did not help.

This case highlights the strong feelings of guilt that can be brought out by genetic diseases and the great need for high-quality psychological support for the index patient and at-risk relatives. Another major issue, illustrated by this case, is whether an individual found to carry a *TTR* mutation or his/her physician has a moral/ethical responsibility to inform at-risk relatives of their genetic disease risk. For the physician, the consequences of breaching doctor–patient confidentiality by unauthorized disclosure of genetic risk to a patient’s relatives and the consequences of withholding disease risk information from relatives should be weighed thoroughly.<sup>23</sup> Each case should be considered on its own merits according to the *TTR* mutation, familial disease characteristics, and available medical interventions, and should be balanced against the social and psychological costs.

*Need for Flexibility in Timing of Genetic Testing.* Case 2: An asymptomatic 35-year-old woman and mother of 2 asked for genetic testing, after 1 parent and 1 sibling tested positive for the *TTR* Ser50Arg (p.Ser70Arg) mutation. She underwent psychological and genetic counseling before testing. When the test result showed she carried the mutation, she refused to return to the clinic, not even for psychological support. Three years later, when neuropathic symptoms developed, she asked for readmission to the clinic.

This illustrates that the timing between the diagnosis of the index patient and the offer of genetic testing to interested family members should be flexible. Consistent with the Wilson and Jungner classic screening criteria, identification of carriers should be a continuing process and not a “once-and-for-all” project.<sup>24,25</sup>

*Deferment of Genetic Testing until Adulthood.* Case 3: A 29-year-old woman faced a dilemma: on the one hand, she wanted to know if her daughters (3 and 6 years old) had inherited the *TTR* Gly47Ala gene from her husband, who died of advanced cardiomyopathy and arrhythmia at age 38. On the other hand, the mother was concerned about the impact on family dynamics if the test results were to differ between the daughters, fearing she may raise them differently. She followed recommendations to

defer testing until the girls were 18 years old. The daughters returned 16 years later to take the test, and were both negative. Yet, the mother had lived in fear and uncertainty for 16 years.

Case 4: A 40-year-old liver transplant recipient with TTR-FAP due to a *TTR* Val30Met (p.Val50-Met) mutation, and an extensive family history of the condition, and his 39-year-old wife wanted to know whether their newborn child carried the mutation. They wished to have a second child, but only if their first baby’s test was negative. The healthcare team educated the parents on new drug developments, but the couple still insisted on testing the baby.

Genetic testing of children for a future risk of developing TTR-FAP, featured in cases 3 and 4 above, is controversial,<sup>26,27</sup> and is forbidden by law in some countries. Professional organizations worldwide are largely unanimous in recommending deferment of genetic testing for adult-onset conditions until the test subject is competent to provide informed consent, unless there is a preventive intervention or treatment available to children at the time of testing.<sup>25,28,29</sup> Consistently, we discourage genetic testing for TTR-FAP before age 18, as there is no medical benefit from determining carrier status in childhood. In the future, it is possible that the optimal age for genetic screening for TTR-FAP could decrease due to advances in disease-modifying therapies. Indeed, considering that aggregation of variant TTR is likely to begin long before appearance of clinical symptoms or detectable laboratory abnormalities, perhaps from the moment of conception, developing effective, safe, and inexpensive prevention at the presymptomatic stage should be a focus of future research efforts.

Prenatal genetic testing for TTR-FAP followed by selective abortion and pre-implantation genetic diagnosis are feasible and may be an option for some families.<sup>30–32</sup> Perspectives on the routine use of these methods to eradicate TTR-FAP may differ among healthcare providers and families, depending on age of onset and penetrance in the family/population, and with recent and future advances in disease management.

#### **PREDICTIVE TESTING PROTOCOLS FOR TTR-FAP**

For maximum benefit and minimal risk, predictive testing for TTR-FAP must be performed in conjunction with adequate pre- and posttest genetic counseling.<sup>17,18,33</sup> To enable individuals considering a genetic test to make well-informed choices, they must be educated on the nature and consequences of TTR-FAP and receive psychosocial support to help them fully understand and carefully consider all potential implications of test

results. The more information individuals receive before genetic testing, the better they appear to cope with the test results; information should be individualized based on specific experience, knowledge, needs, expectations, personal beliefs and values.<sup>33</sup> A comprehensive set of guidelines for genetic counseling for adult-onset conditions, specifying minimum standards of care and ethical, practical, and psychosocial issues to be considered, have been devised recently.<sup>18</sup>

Brazilian and Portuguese predictive testing protocols for severe late-onset neurodegenerative disorders, including TTRVal30Met-FAP, have been published.<sup>16</sup> The screening protocols for TTR-FAP in Brazil and Portugal, along with those of Mexico, Argentina, Germany, and Italy, all involve a multidisciplinary team, 1–4 pre-test sessions, and comparable post-disclosure follow-up procedures (Table 2). Depending on symptoms, additional specialists may apply for consultations.

#### **DISEASE RISK ESTIMATION AND THE PREDICTIVE VALUE OF GENETIC TESTING FOR TTR-FAP**

Estimation of the age-specific risk that TTR-FAP will manifest in mutation carriers (penetrance) is important for informed decision-making and appropriate interpretation of positive genetic test results. Conveying accurate risk information is challenging, as TTR-FAP is a highly heterogeneous disease with substantial variation in age at onset, organ involvement, disease expressivity, and penetrance, depending on the pathogenic *TTR* mutation and other ill-defined/unknown genetic, epigenetic, and environmental factors.<sup>1,2,34,35</sup> Consequently, knowing that an individual carries a *TTR* mutation leaves some uncertainty regarding the exact risk of developing clinical symptoms, when they may appear, their nature, and severity. Nevertheless, predictive genetic testing provides more accurate risk assessments than family history alone and allows appropriate targeting of multidisciplinary screening and surveillance strategies.

Published age-dependent risk estimates differ across *TTR* mutations and countries (Table 3).<sup>36–41</sup> Penetrance estimates range from 22% at age 60 and 69% at age 90 in Swedish carriers of the *TTR* Val30Met mutation to 89% at age 60 and 91% at age 80 in families of Portuguese ancestry harboring the same mutation.<sup>38–40</sup> These estimates suggest that, although the majority of carriers will develop TTR-FAP, some may remain asymptomatic for their whole lives. The predictive power of genetic testing will be highest in populations with early onset and high penetrance.

There are clear intrafamilial correlations in age of onset,<sup>38,42</sup> and the distribution of age of onset,

including the age of unaffected heterozygotes in the family, should be considered in age-dependent risk estimations.<sup>43</sup> Potential gender differences, parent-of-origin effects, and genetic anticipation (earlier age of onset and increased severity in successive generations), as observed in the age of onset of TTR-FAP in Portuguese families who harbor a Val30Met mutation,<sup>7,37,42</sup> also must be taken into consideration. Thus, an analysis of 926 Portuguese parent–offspring pairs showed the mean onset age was significantly lower in men than women (approximately 4-year difference for sons vs. daughters, and for fathers vs. mothers), and anticipation was most prominent among mother–son pairs [mean (SD): 10.4 (9.3) years] and least marked among father–daughter pairs [mean (SD): 1.2 (9.8) years].<sup>42</sup> Methods to estimate an age-dependent penetrance function from a sample of heterozygotes for a *TTR* mutation based on disease status and genotypic information have been published.<sup>38,44</sup>

Notably, pioneer studies in Val30Met carriers have revealed significant associations between age of onset and different single nucleotide polymorphisms (SNPs) in plasma retinol-binding protein 4 (*RBP4*, metabolically interacts with *TTR*), amyloid P component serum (*APCS*, non-fibrillar components of amyloid deposits), and androgen receptor (*AR*, affects *TTR* expression) genes.<sup>45,46</sup> It could be envisioned that future, more detailed analysis of genomes and epigenomes of TTR-FAP mutation carriers may establish mutation signatures in susceptibility/modifier genes associated with particular subtypes of TTR-FAP. This could help to better predict possible age of onset and guide medical management.

#### **STRUCTURED CLINICAL FOLLOW-UP OF CARRIERS OF TTR-FAP MUTATIONS**

Disease-modifying treatments have only been tested in clinically symptomatic TTR-FAP, and pre-symptomatic treatment of gene carriers is not an accepted indication at this time. To allow initiation of treatment at the earliest possible time, gene carriers should be monitored regularly for early signs/symptoms, including progressive symmetric sensory–motor neuropathy, autonomic dysfunction (e.g., heart rate variation, erectile dysfunction, postural hypotension, cardiac conduction defects), GI complaints (e.g., alternating diarrhea and constipation, chronic diarrhea or constipation, nausea, vomiting), unexplained weight loss, cardiac hypertrophy, arrhythmias, cardiomyopathy, bilateral carpal tunnel syndrome, renal abnormalities, or ophthalmologic manifestations (e.g., dry eye, glaucoma, vitreous opacities). The frequency of screening visits should take into account the individual's

age relative to projected symptom onset based on *TTR* mutation and family history. Annual monitoring is standard.

Neurological screening at periodic follow-up visits should include as many of the following tests as are available: neurological examination;

**Table 2.** Comparison of genetic testing protocols for *TTR*-FAP in asymptomatic, adult ( $\geq 18$  years), first-degree (50% risk) relatives of patients diagnosed with *TTR*-FAP.

	Portugal* <sup>16</sup>	Brazil* <sup>16</sup>	Argentina	Germany	Mexico	Italy
<b>Team</b>						
Amyloid specialist	—	—	—	—	—	+
Clinical geneticist (CG)	+	+	+	+	+	+
Genetic counselor (GC)	+	+	—	+	—	—
Hepatologist	—	—	—	+	—	—
Neurologist (N)	+	+	+	+	+	—
Psychologist	+	+	—	—	—	—
Psychiatrist (PSY)	+	+	+	—	—	+ <sup>‡</sup>
Social worker (SW)	+	—	—	—	—	—
<b>Pre-test visits</b>						
Standard number of pre-test visits (interval)	2 (3 wk)	4 (1–2 wk)	1	1	2 (3 wk)	1 <sup>§</sup>
<b>Standard pre-test sessions</b>						
General information on <i>TTR</i> -FAP	—	—	1+	1+	—	—
Genetic counseling	2+	2+	1+	1+	1+	1+
Psychological evaluation	1+	2+ <sup>  </sup>	—	—	—	—
Social evaluation	1+	—	—	—	—	—
Blood collection	2+	1+	1+	1+	—	1+
Saliva collection	—	—	—	—	1+	—
Team discussion about consultation	—	—	—	—	—	1+
Signed informed consent	Yes	No	No	Yes	Yes	Yes
Additional sessions upon referral or request	N, PSY, SW	N, PSY	PSY	N, C	N	PSY
<b>Posttest visits</b>						
Disclosure of results	Third visit	Fifth visit	Second visit	Second visit <sup>¶</sup>	Third visit	Second visit
<b>Standard post-disclosure follow-ups if result positive</b>						
Baseline assessment	—	—	N, PSY	N, C	N, C	N, C
<b>Follow-ups</b>						
Phone contact <sup>#</sup>	—	—	—	—	—	1 and 6 mo
Psychologist or psychiatrist <sup>#</sup>	3 wk, 6 mo, and 1 y	3 wk, 6 mo, and 1 y	Biannually	—	—	—
Neurologist	1 y	—	Biannually	Annually	Annually	Annually
Cardiologist	—	—	—	Annually	Annually	Annually
Additional follow-ups upon request	CG, GC, SW	CG, GC, N, SW	CG, PSY	NEP, OPH, PSY, SW	GC,** NUT, OPH, PSY, TP	PSY

C, cardiologist; CG, clinical geneticist; —, item not applicable; GC, genetic counselor; mo, months; NEP, nephrologist; N, neurologist; NUT, nutrition; OPH, ophthalmologist; PSY, psychiatrist; SW, social worker; TP, transplant protocol; wk, weeks; y, years.

\*These protocols are based on formal guidelines for predictive testing for Huntington's disease, which incorporate lessons from decades of careful research and evaluation.<sup>16,17</sup>

<sup>†</sup>Individuals at 25% risk may be accepted for predictive testing if the potential transmitting parent is unavailable. Individuals aged  $\geq 16$  years may also be tested if reproductive decisions, including prenatal diagnosis, need to be made.<sup>16</sup>

<sup>‡</sup>As clinician supervisor.

<sup>§</sup>May be increased to 2 visits at least 2 weeks apart according to the judgment of the specialists after the first consultation.

<sup>||</sup>Psychological assessment at second visit and a follow-up by psychologist or psychiatrist at third visit.

<sup>¶</sup>Results are personally communicated and discussed.

<sup>#</sup>These follow-ups also apply if the test result is negative.

\*\*Genetic counseling by clinical geneticist or neurologist.

**Table 3.** Age-dependent penetrance estimates for French, Portuguese, and Swedish carriers of TTR-FAP mutations.

	Penetrance estimate (95% confidence interval), at age		
	50 years	60 years	80 years
Val30Met, Portuguese cases <sup>38*</sup>	0.80 (0.75–0.85)	0.89 (0.85–0.94)	0.91 (0.86–0.95)
Non-Val30Met, French cases <sup>38</sup>	0.22 (0.17–0.26)	0.48 (0.40–0.55)	0.95 (0.92–0.98)
Val30Met, French cases <sup>38</sup>	0.14 (0.10–0.17)	0.29 (0.22–0.36)	0.73 (0.62–0.83)
Val30Met, Swedish cases <sup>39</sup>	0.11 (0.08–0.16)	0.22 (0.16–0.29)	0.52 (0.42–0.63)

\*All Portuguese patients were seen at a French hospital (Bicêtre Hospital), and Portuguese refers to ancestry rather than country of residence. Most (43 of 48, 90%) of the Portuguese index cases presented with early-onset disease (i.e., initial symptoms appeared before age 50 years).<sup>38</sup>

quantitative sensory testing; electromyography with nerve conduction studies; sympathetic skin response; and autonomic evaluations, including postural blood pressure monitoring, heart rate response to deep breathing, and a symptom questionnaire (incorporating GI and sexual dysfunction) (Fig. 2). Additional small-fiber neurophysiological tests, such as laser evoked potentials or sudomotor testing, should be applied in cases of doubtful disease-related symptoms. Several scales are used to evaluate and monitor neuropathic symptoms, such as the Norfolk Quality of Life–Diabetic Neuropathy questionnaire or Neuropathy Impairment Score.<sup>47,48</sup> Autonomic symptoms may be evaluated with the Compound Autonomic Dysfunction Test or COMPASS 31.<sup>49,50</sup> In addition, cardiac [echocardiography, electrocardiography, brain natriuretic peptide (BNP) or N-terminal pro-hormone BNP

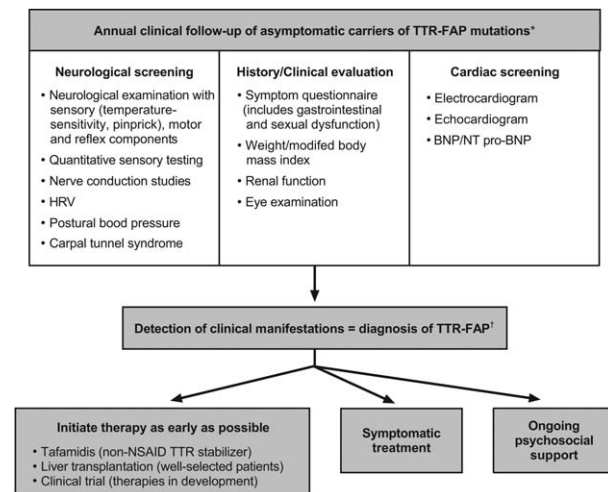
(NT pro-BNP)], ophthalmologic, and renal screening should be performed.

### CONFIRMATION OF SYMPTOMATIC DISEASE ONSET IN CONFIRMED GENE CARRIERS

Diagnosis of symptomatic TTR-FAP and treatment initiation in gene carriers should occur upon manifestation of the earliest detectable disease sign/symptom.<sup>6</sup> Due to the highly heterogeneous, multisystemic nature, and nonspecific symptoms of TTR-FAP, clinical judgment is required to confirm the onset of symptomatic disease in gene carriers.

At present, diagnosis is based on medical history, physical examination, and abnormalities or change from baseline in screening tests, such as impaired nerve conduction, bilateral sensory abnormalities indicative of peripheral neuropathy detected by quantitative sensory testing, echocardiographic abnormalities (e.g., interventricular septum thickness >12 mm without a history of high blood pressure), conduction defects, arrhythmias on electrocardiography, unexplained weight loss or decrease in modified body mass index, and presence of autonomic symptoms (e.g., reduced heart rate variability, GI problems, sexual dysfunction). At the discretion of the treating physician,  $\geq 2$  serial abnormal readings demonstrating progression a combination of  $\geq 2$  different abnormalities may be required to ascertain the diagnosis of TTR-FAP. Objective evidence of neuropathy, such as a progressive reduction in sensory nerve action potentials, can be considered sufficient to reach a diagnosis of TTR-FAP in gene carriers.

Biopsy confirmation of amyloid deposits (e.g., by labial salivary gland biopsy)<sup>51</sup> can corroborate a diagnosis. However, a negative biopsy finding does not exclude the existence of amyloid deposits given a non-negligible false-negative rate. Therefore, a positive result may not be mandatory to confirm a diagnosis of TTR-FAP in clinically symptomatic carriers of TTR-FAP mutations (unless they have a concomitant condition that could be responsible for the symptoms). Nonetheless, biopsy confirmation before initiation of treatment or liver transplantation is currently standard practice or a legal/regulatory requirement in some countries.



**FIGURE 2.** Structured clinical follow-up of asymptomatic carriers of TTR-FAP mutations. \*Consider more frequent monitoring and inclusion of additional tests if there is suspicion the subject may be converting to symptomatic disease, or if the subject approaches the projected age of onset based on TTR mutation and family history. †Diagnosis may be confirmed by biopsy for amyloid deposits, but a negative finding does not exclude a diagnosis. BNP, brain natriuretic peptide; HRV, heart rate variability; NSAID, non-steroidal anti-inflammatory drug; NT pro-BNP, N-terminal pro-hormone brain natriuretic peptide; TTR-FAP, transthyretin familial amyloid polyneuropathy.

With further research on early detection and risk evaluation, consensus recommendations and/or criteria should be developed around the initiation of disease-modifying therapy before detectable amyloid deposits or clinical symptoms.

## CONCLUSIONS

Genetic testing for TTR-FAP in at-risk individuals and regular clinical surveillance for early detection of clinical symptom onset in gene carriers allows therapeutic intervention before accumulation of substantial and irreversible damage. Such management of asymptomatic carriers is important and, recently (as the current paper was being finalized), a European expert group published consensus recommendations.<sup>52</sup> Procedures must be continually adapted to reflect advances in our knowledge and changes in the treatment options available. Presymptomatic treatment of gene carriers is not currently an accepted indication, but may become a means of delaying or preventing the onset of TTR-FAP in the future.

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